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(71) Applicant: NORWICH EATON PHARMACEUTICALS, INC. [US/US]; 17 Eaton Avenue, Norwich, NY 13815 (US).

(72) Inventors: DEMUTH, Thomas, Prosser, Jr. ; RD4, Box 161, Norwich, NY 13815 (US). WHITE, Ronald, Eugene ; Star Route Box 214, South Plymouth, NY 13844 (US).

(74) Agents: WITTE, Monte, Dale et al.; The Procter & Gamble Company, Winton Hill Technical Company, 6060 Center Hill Road, Cincinnati, OH 45224 (US).

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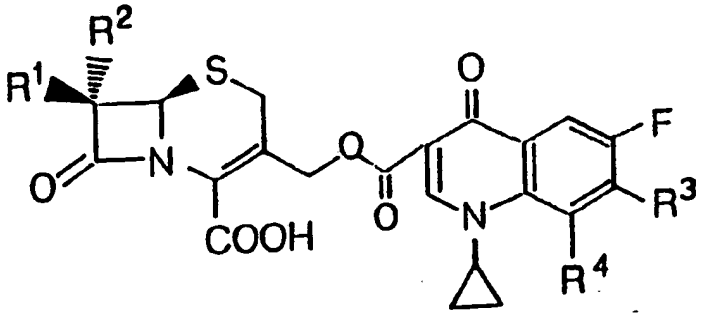

(I)

(57) Abstract

Antimicrobial fluoroquinolonyl cephems of formula (I), wherein (1) R^1 and R^2 are groups among those known in the art for substitution at the 7-positi n of an antimicrobially-active cephem; (2) R^3 is a substituted or unsubstituted, nitrogen-containing, heterocyclic moiety; and (3) R^4 is hydr gen, halogen, lower alkoxy or cyclic alkoxy, amino, nitro or cyan . Preferably, R^3 is substituted or unsubstitued piperazine, 3-aminopyrrolidine, r 3-aminomethylpyrrolidine. R^4 is preferably hydrogen or halogen.

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NOVEL ANTIMICROBIAL FLUOROQUINOLONYL CEPHEMS

This application is a continuation-in-part of U.S. Patent Application Serial No. 261,949, filed October 24, 1988.

BACKGROUND OF THE INVENTION

This invention relates to novel antimicrobial compounds and compositions. The compounds of this invention contain a quinolone moiety and a cephem moiety, in a new chemical entity.

The chemical and medical literature describes a myriad of compounds that are said to be antimicrobial, i.e., capable of destroying or suppressing the growth or reproduction of microorganisms, such as bacteria. In particular, antibacterials include a large variety of naturally-occurring (antibiotic), synthetic, or semi-synthetic compounds. They may be classified (for example) as the aminoglycosides, ansamacrolides, beta-lactams (including penicillins and cephalosporins), lincosaminides, macrolides, nitrofurans, nucleosides, oligosaccharides, peptides and polypeptides, phenazines, polyenes, polyethers, quinolones, tetracyclines, and sulfonamides. Such antibacterials and other antimicrobials are described in Antibiotics, Chemotherapeutics, and Antibacterial Agents for Disease Control (M. Grayson, editor, 1982), and E. Gale et al., The Molecular Basis of Antibiotic Action 2d edition (1981), both incorporated by reference herein.

The mechanism of action of these antibacterials vary. However, each can be generally classified as functioning in one or more of four ways: by inhibiting cell wall synthesis or repair; by altering cell wall permeability; by inhibiting protein synthesis; or by inhibiting synthesis of nucleic acids. For example, beta-lactam antibacterials act through inhibiting the

essential penicillin binding proteins (PBPs) in bacteria, which are responsible for cell wall synthesis. On the other hand, quinolones act by inhibiting synthesis of bacterial DNA, thus preventing the bacteria from replicating.

Not surprisingly, the pharmacological characteristics of antibacterials and other antimicrobials, and their suitability for any given clinical use, also vary considerably. For example, the classes of antimicrobials (and members within a class) may vary in their relative efficacy against different types of microorganisms, and their susceptibility to development of microbial resistance. These antimicrobials may also differ in their pharmacological characteristics, such as their bioavailability, and biodistribution. Accordingly, selection of an appropriate antibacterial (or other antimicrobial) in any given clinical situation can be a complicated analysis of many factors, including the type of organism involved, the desired method of administration, and the location of the infection to be treated.

The development of microbial resistance is one factor in the selection of an appropriate antimicrobial (particularly antibacterials), which is of increasing concern in medical science. This "resistance" can be defined as existence of organisms, within a population of a given microbial species, that are less susceptible to the action of a given antimicrobial agent. Such resistant strains may subvert the mechanism of action of a particular antimicrobial, or chemically degrade the antimicrobial before it can act. For example, bacterial resistance to beta-lactam antibacterials has arisen through development of bacterial strains that produce beta-lactamase enzymes, which degrade the antibacterial.

In part as a result of the intense use of antibacterials over extended periods of time, many highly resistant strains of bacteria have evolved. This is of particular concern in environments such as hospitals and nursing homes, which are characterized by relatively high rates of infection and intense use of antibacterials. See, e.g., W. Sanders, Jr. et al.,

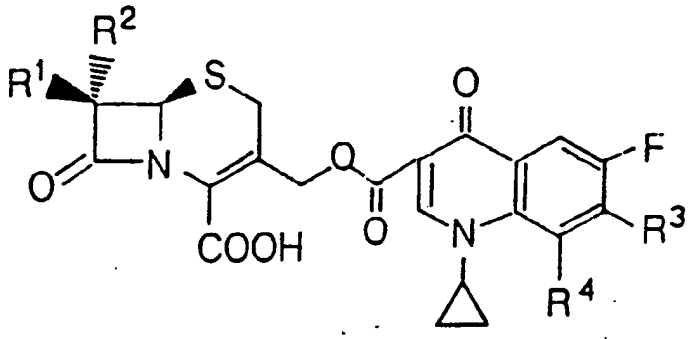
"Inductible Beta-lactamases: Clinical and Epidemiologic Implications for Use of Newer Cephalosporins", 10 Reviews of Infectious Diseases 830 (1988). Indeed, the development of resistant bacterial strains has led to a concern that pathogenic bacteria may be produced that are essentially resistant to even the newest developed antibacterial agents.

The literature describes many attempts to enhance the efficacy of antimicrobials, and to overcome the development of microbial resistance. Many such attempts involve the combination of antimicrobials. For example, Thabaut et al., 16 Presse Med. 2167 (1987) describes combinations of pefloxacin (a quinolone) with the beta-lactams cefotaxime and cefsulodin. Lenoc et al., 36 Path. Biol. 762 (1988), describes combined use of cephems with aminoglycosides, and with quinolones. Japanese Patent Publication 60/06,617, published January 14, 1985, also describes compositions containing beta-lactams and quinolones. O'Callaghan et al., 10 Antimicrobial Agents and Chemotherapy 245 (1976), describes a mercapto pyridine-substituted cephem, which is said to liberate an active antimicrobial agent when the cephalosporin is hydrolyzed by beta-lactamase. Mobashery et al., 108 J. American Chemical Society 1684 (1986), presents a theory of employing bacterial beta-lactamase in situ to release an antibacterially-active leaving group from the 10-position of a cephem.

However, many such attempts to produce improved antimicrobials yield equivocal results. Indeed, few antimicrobials are produced that are truly clinically-acceptable in terms of their spectrum of antimicrobial activity, avoidance of microbial resistance, and pharmacology.

SUMMARY OF THE INVENTION

The present invention provides compounds of the formula:



wherein

(A) R^1 is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, R^{10a}-O-, R^{10a}CH=N-, $(R^{10})(R^{11})$N-, R^{12}-C(=CHR^{15})-C(=O)NH-, R^{12}-C(=NO-R^{14})-C(=O)NH-, or R^{13}-$(CH_2)_m$-C(=O)NH-; where

(1) m is an integer from 0 to 9;

(2) R^{10} and R^{11} are, independently, R^{10a} where R^{10a} is hydrogen, alkyl, alkenyl, carbocyclic ring, or heterocyclic ring substituents; or R^{10} and R11 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(3) R^{12} is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring;

(4) R^{13} is R^{12}, -Z^1, or -CH(Z^2)(R^{12});

(5) R^{14} is R^{12}, arylalkyl, heteroarylalkyl, -C(R^{17})(R^{18})COOH, -C(=O)O-R^{12}, or -C(=O)NH-R^{12}, where R^{17} and R^{18} are, independently, R^{12} or together comprise a carbocyclic ring or a heterocyclic ring including the carbon atom to which R^{17} and R^{18} are bonded;

(6) R^{15} is R^{14}, halogen, -Z^1, or -CH(Z^2)(R^{12});

(7) Z^1 is -C(=O)OR^{16}, -C(=O)R^{16}, -N(R^{19})R^{16}, -S(O)$_p$$R^{24}$, or -O$R^{24}$; and Z^2 is Z^1 or -OH, -SH, or -SO_3H;

(a) p is an integer from 0 to 2;

(b) R^{19} is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; -SO_3H; -C(=O)R^{20}; or, when R^{13} is -CH(Z^1)(R^{12}) and Z^1 is -N(R^{19})R^{16}, R^{19} may

comprise a moiety bonded to R^{16} to form a heterocyclic ring; and

(c) R^{20} is R^{12}, $NH(R^{12})$, $N(R^{12})(R^{21})$, $O(R^{21})$, or $S(R^{21})$; where R^{21} is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or when R^{20} is $N(R^{12})(R^{21})$ R^{21} may be a moiety bonded to R^{12} to form a heterocyclic ring; and

(8) R^{16} is R^{24} or hydrogen; where R^{24} is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Z^1 is $N(R^{19})R^{16}$ and R^{16} is R^{24}, R^{16} and R^{19} may together comprise a heterocyclic ring including the nitrogen atom to which R^{19} is bonded;

(B) R^2 is hydrogen, halogen, alkoxy, or $R^{22}C(=O)NH-$, where R^{22} is hydrogen or alkyl;

(C) R^3 is a nitrogen-containing heterocyclic ring; and

(D) R^4 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl or $N(R^{10})(R^{11})$;

and the pharmaceutically-acceptable salts and biohydrolyzable esters thereof, and hydrates thereof.

It has been found that the compounds of this invention, and compositions containing these compounds, are effective antimicrobial agents against a broad range of pathogenic microorganisms. These compounds provide advantages versus antimicrobial agents among those known in the art, including (for example) the spectrum of antimicrobial activity, potency, the avoidance of microbial resistance, and reduced toxicity.

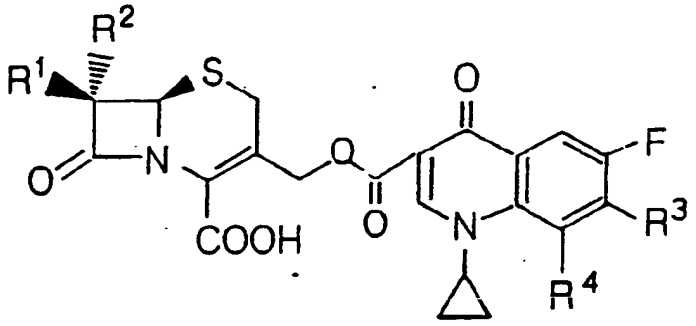
DESCRIPTION OF THE INVENTION

The present invention encompasses certain novel fluoroquinolonyl cephems, methods for their manufacture, dosage forms, and methods of administering the fluoroquinolonyl cephems to a human or other animal subject. Specific compounds and compositions to be used in the invention must, accordingly, be pharmaceutically acceptable. As used herein, such a "pharmaceutically-acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side

effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

Fluoroquinolonyl Cephems:

The compounds of this invention, herein referred to as "fluoroquinolonyl cephems", are of the formula:



wherein

(A) R^1 is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, R^{10a}-O-, $R^{10a}CH=N$-, $(R^{10})(R^{11})N$-, R^{12}-C(=CHR^{15})-C(=O)NH-, or (preferably) R^{12}-C(=NO-R^{14})-C(=O)NH-, or R^{13}-$(CH_2)_m$-C(=O)NH-; where

(1) m is an integer from 0 to 9 (preferably from 0 to 3);

(2) R^{10} and R^{11} are, independently, R^{10a} where R^{10a} is hydrogen, alkyl, alkenyl, carbocyclic ring, or heterocyclic ring substituents; or R^{10} and R11 together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(3) R^{12} is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring (preferably alkyl, a carbocyclic ring, or a heterocyclic ring);

(4) R^{13} is R^{12}, -Z^1, or -CH(Z^2)(R^{12});

(5) R^{14} is R^{12}, arylalkyl, heteroarylalkyl, -C(R^{17})(R^{18})COOH, -C(=O)O-R^{12}, or -C(=O)NH-R^{12}, where R^{17} and R^{18} are, independently, R^{12} or together comprise a carbocyclic ring or a heterocyclic ring including the carbon atom to which R^{17} and R^{18} are bonded (preferably R^{12} or -C(R^{17})(R^{18})COOH);

(6) R^{15} is R^{14}, halogen, -Z^1, or -CH(Z^2)(R^{12}) (preferably R^{14} or halogen);

(7) Z^1 is $-C(=O)OR^{16}$, $-C(=O)R16$, $-N(R^{19})R^{16}$, $-S(O)_pR^{24}$, or $-OR^{24}$; and Z^2 is Z^1 or -OH, -SH, or $-SO_3H$;

(a) p is an integer from 0 to 2 (preferably 0);

(b) R^{19} is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; $-SO_3H$; $-C(=O)R^{20}$; or, when R^{13} is $-CH(Z^1)(R^{12})$ and Z^1 is $-N(R^{19})R^{16}$, R^{19} may comprise a moiety bonded to R^{16} to form a heterocyclic ring; and

(c) R^{20} is R^{12}, $NH(R^{12})$, $N(R^{12})(R^{21})$, $O(R^{21})$, or $S(R^{21})$ (preferably R^{12}, $NH(R^{12})$, or $N(R^{12})(R^{21})$); where R^{21} is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or (preferably) when R^{20} is $N(R^{12})(R^{21})$ R^{21} may be a moiety bonded to R^{12} to form a heterocyclic ring; and

(8) R^{16} is R^{24} or hydrogen; where R^{24} is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Z^1 is $N(R^{19})R^{16}$ and R^{16} is R^{24}, R^{16} and R^{19} may together comprise a heterocyclic ring including the nitrogen atom to which R^{19} is bonded (preferably hydrogen, alkyl, a carbocyclic ring or a heterocyclic ring);

(B) R^2 is hydrogen, halogen, alkoxy, or $R^{22}C(=O)NH-$ (preferably hydrogen or alkoxy), where R^{22} is hydrogen or alkyl (preferably hydrogen);

(C) R^3 is a nitrogen-containing heterocyclic ring; and

(D) R^4 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl or $N(R^{10})(R^{11})$ (preferably hydrogen or halogen);

and the pharmaceutically-acceptable salts and biohydrolyzable esters thereof, and hydrates thereof.

Definitions and Usage of Terms:

The following is a list of definitions for terms used herein.

"Heteroatom" is a nitrogen, sulfur or oxygen atom. Groups containing one or more heteroatoms may contain different heteroatoms.

"Alkyl" is an unsubstituted or substituted saturated hydrocarbon chain radical having from 1 to 8 carbon atoms, preferably from 1 to 4 carbon atoms. Preferred alkyl groups include (for example) methyl, ethyl, propyl, isopropyl, and butyl.

"Heteroalkyl" is an unsubstituted or substituted saturated chain radical having from 3 to 8 members comprising carbon atoms and one or two heteroatoms.

"Alkenyl" is an unsubstituted or substituted hydrocarbon chain radical having from 2 to 8 carbon atoms, preferably from 2 to 4 carbon atoms, and having at least one olefinic double bond.

"Carbocyclic ring" is an unsubstituted or substituted, saturated, unsaturated or aromatic, hydrocarbon ring radical. Carbocyclic rings are monocyclic or are fused, bridged or spiro polycyclic ring systems. Monocyclic rings contain from 3 to 9 atoms, preferably 3 to 6 atoms. Polycyclic rings contain from 7 to 17 atoms, preferably from 7 to 13 atoms.

"Cycloalkyl" is a saturated carbocyclic ring radical. Preferred cycloalkyl groups include (for example) cyclopropyl, cyclobutyl and cyclohexyl.

"Heterocyclic ring" is an unsubstituted or substituted, saturated, unsaturated or aromatic ring radical comprised of carbon atoms and one or more heteroatoms in the ring. Heterocyclic rings are monocyclic or are fused, bridged or spiro polycyclic ring systems. Monocyclic rings contain from 3 to 9 atoms, preferably 3 to 6 atoms. Polycyclic rings contain from 7 to 17 atoms, preferably from 7 to 13 atoms.

"Aryl" is an aromatic carbocyclic ring radical. Preferred aryl groups include (for example) phenyl, tolyl, xylyl, cumenyl and naphthyl.

"Heteroaryl" is an aromatic heterocyclic ring radical. Preferred heteroaryl groups include (for example) thienyl, furyl, pyrrolyl, pyridinyl, pyrazinyl, thiazolyl, pyrimidinyl, quinolinyl, and tetrazolyl.

"Alkoxy" is an oxygen radical having a hydrocarbon chain substituent, where the hydrocarbon chain is an alkyl or alkenyl

(i.e., -O-alkyl or -O-alkenyl). Preferred alkoxy groups include (for example) methoxy, ethoxy, propoxy and allyloxy.

"Alkylamino" is an amino radical having one or two alkyl substituents (i.e., -N-alkyl).

"Arylalkyl" is an alkyl radical substituted with an aryl group. Preferred arylalkyl groups include benzyl and phenylethyl.

"Arylamino" is an amine radical substituted with an aryl group (i.e., -NH-aryl).

"Aryloxy" is an oxygen radical having a aryl substituent (i.e., -O-aryl).

"Acyl" or "carbonyl" is a radical formed by removal of the hydroxy from an carboxylic acid (i.e., R-C(=O)-). Preferred alkylacyl groups include (for example) acetyl, formyl, and propionyl.

"Acyloxy" is an oxygen radical having an acyl substituent (i.e., -O-acyl); for example,-O-C(=O)-alkyl.

"Acylamino" is an amino radical having an acyl substituent (i.e., -N-acyl); for example, -NH-C(=O)-alkyl.

"Halo", "halogen", or "halide" is a chloro, bromo, fluoro or iodo atom radical. Chloro and fluoro are preferred halides.

Also, as referred to herein, a "lower" hydrocarbon moiety (e.g., "lower" alkyl) is a hydrocarbon chain comprised of from 1 to 6, preferably from 1 to 4, carbon atoms.

A "pharmaceutically-acceptable salt" is a cationic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino) group. Many such salts are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987 (incorporated by reference herein). Preferred cationic salts include the alkali metal salts (such as sodium and potassium), and alkaline earth metal salts (such as magnesium and calcium). Preferred anionic salts include the halides (such as chloride salts).

A "biohydrolyzable ester" is an ester of a fluoroquinolonyl cephem that does not essentially interfere with the antimicrobial

activity of the compounds, or that are readily metabolized by a human or lower animal subject to yield an antimicrobially-active fluoroquinolonyl cephem. Such esters include those that do not interfere with the biological activity of quinolone antimicrobials or beta-lactam antimicrobials (cephems, for example). Many such esters are known in the art, as described in World Patent Publication 87/05297, Johnston et al., published September 11, 1987, (incorporated by reference herein). Such esters include lower alkyl esters, lower acyloxy-alkyl esters (such as acetoxymethyl, acetoxyethyl, aminocarbonyloxymethyl, pivaloyloxymethyl and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxy-acyloxyalkyl esters (such as methoxycarbonyloxymethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters and alkyl acylamino alkyl esters (such as acetamidomethyl esters).

As defined above and as used herein, substituent groups may themselves be substituted. Such substitution may be with one or more substituents. Such substituents include those listed in C. Hansch and A. Leo, Substituent Constants for Correlation Analysis in Chemistry and Biology (1979), incorporated by reference herein. Preferred substituents include (for example) alkyl, alkenyl, alkoxy, hydroxy, oxo, nitro, amino, aminoalkyl (e.g., aminomethyl, etc.), cyano, halo, carboxy, alkoxyaceyl (e.g., carboethoxy, etc.), thiol, aryl, cycloalkyl, heteroaryl, heterocycloalkyl (e.g., piperidinyl, morpholinyl, pyrrolidinyl, etc.), imino, thioxo, hydroxyalkyl, aryloxy, arylalkyl, and combinations thereof.

Also, as used in defining the structure of the compounds of this invention, a particular radical may be defined for use as a substituent in multiple locations. For example, the R^{10a} substituent is defined as a potential substituent of R^1, but is also incorporated into the definition of other substituents (such as R^4). As used herein, such a radical is independently selected each time it is used (e.g., R^{10a} need not be alkyl in all occurrences in defining a given compound of this invention).

R^1 is any radical that may be substituted at the active stereoisomeric position of the carbon adjacent to the lactam carbonyl of an antimicrobially-active lactam. (As used herein, the term "antimicrobially-active lactam" refers to a lactam-containing compound, without a quinolonyl substituent moiety, which has antimicrobial activity.) This "active" position is beta (i.e., 7-beta) for cephems.

Appropriate R^1 groups will be apparent to one of ordinary skill in the art. Many such R^1 groups are known in the art, as described in the following documents (all of which are incorporated by reference herein): Cephalosporins and Penicillins: Chemistry and Biology (E. Flynn, editor, 1972); Chemistry and Biology of b-Lactam Antibiotics (R. Morin et al., editors, 1987); "The Cephalosporin Antibiotics: Seminar-in-Print", 34 Drugs (Supp. 2) 1 (J. Williams, editor, 1987); New Beta-Lactam Antibiotics: A Review from Chemistry of Clinical Efficacy of the New Cephalosporins (H. Neu, editor, 1982); M. Sassiver et al., in Structure Activity Relationships among the Semi-synthetic Antibiotics (D. Perlman, editor, 1977). W. Durckheimer et al., "Recent Developments in the Field of Beta-Lactam Antibiotics", 24 Angew. Chem. Int. Ed. Engl. 180 (1985); G. Rolinson, "Beta-Lactam Antibiotics", 17 J. Antimicrobial Chemotherapy 5 (1986); European Patent Publication 187,456, Jung, published July 16, 1986; and World Patent Publication 87/05297, Johnston et al., published September 11, 1987.

Preferred R^1 groups are amides, such as: acetylamino, preferably substituted with aryl, heteroaryl, aryloxy, heteroarylthio and lower alkylthio substituents; arylglycylamino, preferably N-substituted with heteroarylcarbonyl and cycloheteroalkylcarbonyl substituents; arylcarbonylamino; heteroarylcarbonylamino; and lower alkoxyiminoacetylamino, preferably substituted with aryl and heteroaryl substituents.

Particularly preferred R^1 groups include amides of the general formula R^{13}-$(CH_2)_m$-C(=O)NH- and R^{13} is R^{12}. Examples of such preferred R^1 groups include:

[(2-amino-5-halo-4-thiazolyl)acetyl]amino;

[(4-aminopyridin-2-yl)acetyl]amino;

[[(3,5-dichloro-4-oxo-1(4H)-pyridinyl)acetyl]amino];

[[[2-(aminomethyl)phenyl]acetyl]amino];

[(1H-tetrazol-1-ylacetyl)amino];

[(cyanoacetyl)amino];

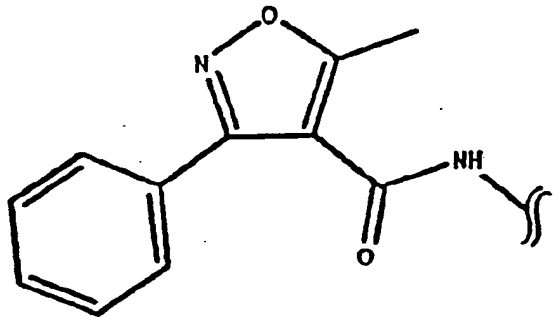
[(2-thienylacetyl)amino];

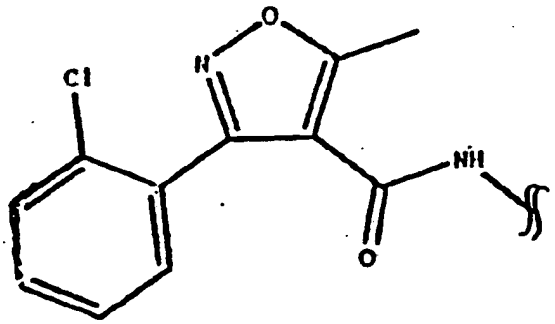
[[(2-amino-4-thiazoyl)acetyl]amino]; and

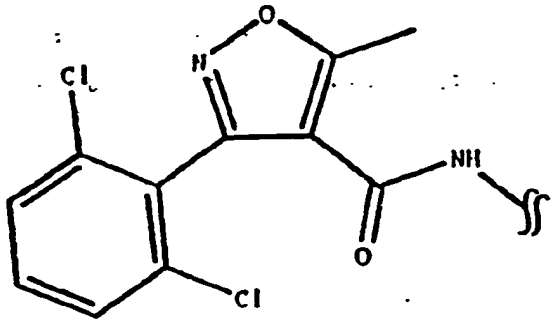
sydnone, 3-[-2-amino]-2-oxoethyl.

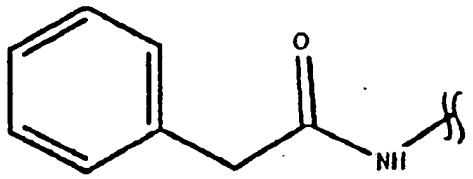
The following are other such preferred R^1 groups.

HCONH-





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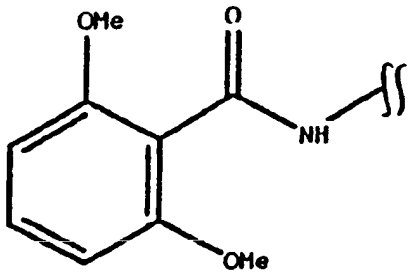
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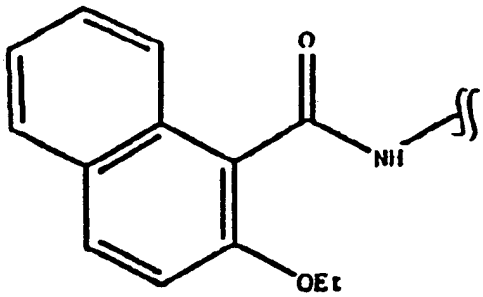
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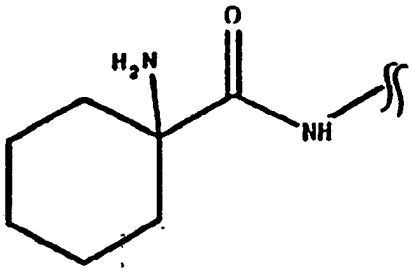
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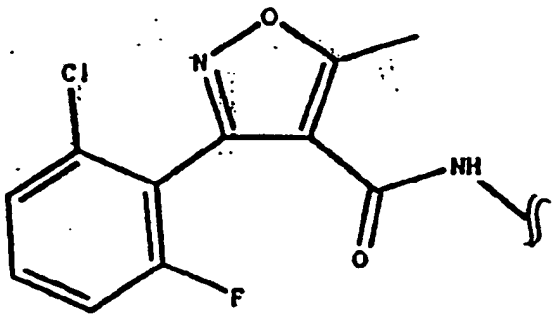
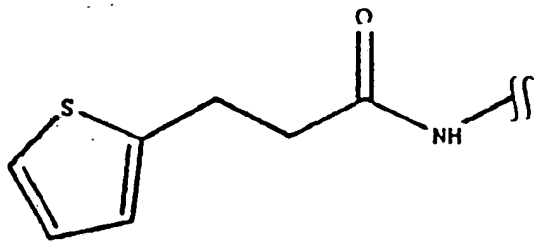
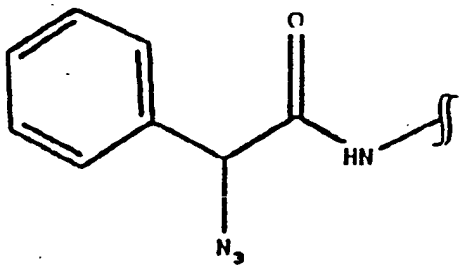
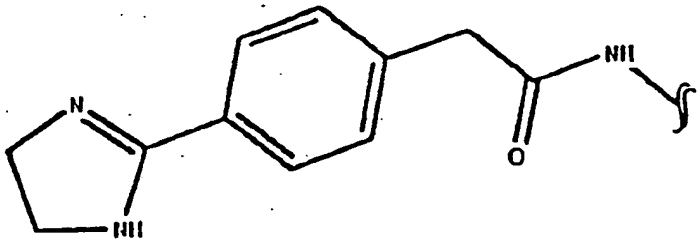
H2N
NH


O
N
Cl
NH
O
F







When R^1 is R^{13}-$(CH_2)_m$-C(C=O)NH-, and R^{13} is -Z^1, preferred R^1 groups include the following:

[sulfamoylphenylacetyl]amino;

[[(4-pyridinylthio)acetyl]amino];

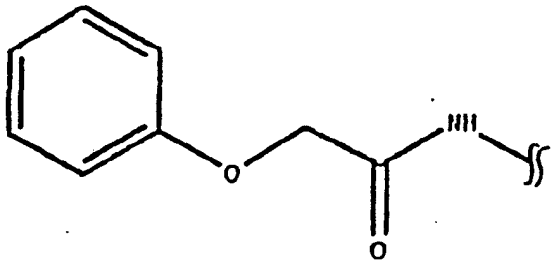
[[[(cyanomethyl)thio]acetyl]amino];

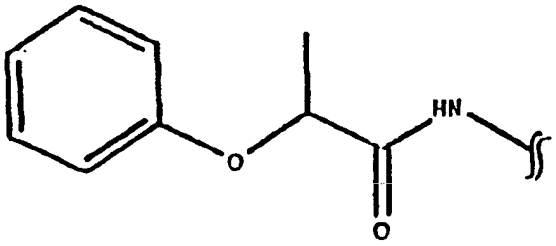
(S)-[[[(2-amino-2-carboxyethyl)thio]acetyl]amino];

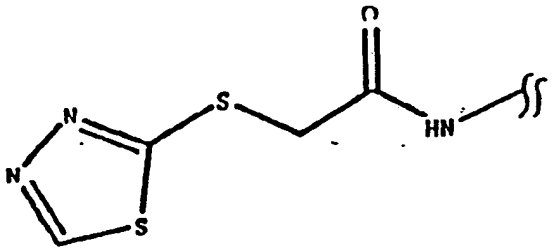
[[[(trifluoromethyl)thio]acetyl]amino]; and

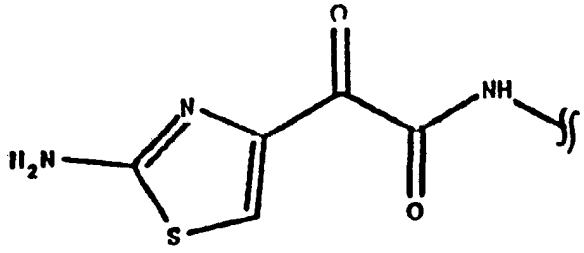
(E)-[[[(2-aminocarbonyl-2-fluoroethenyl)thio]acetyl]amino].

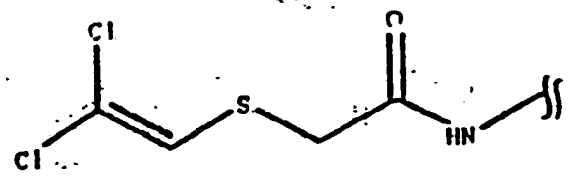
The following are other such preferred R^1 groups.

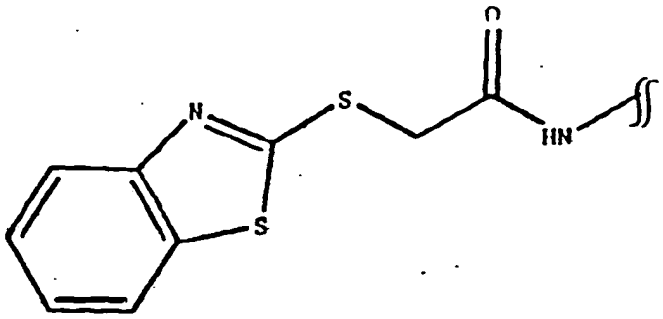


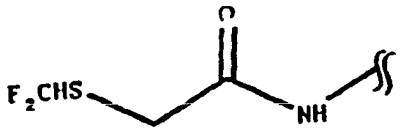


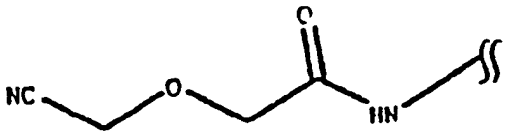


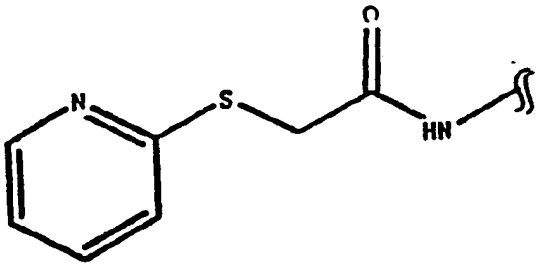


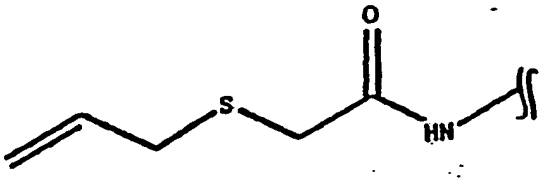








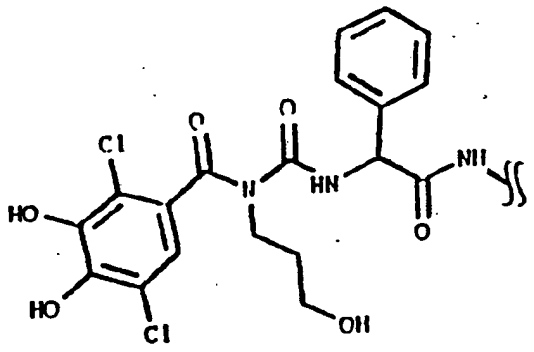


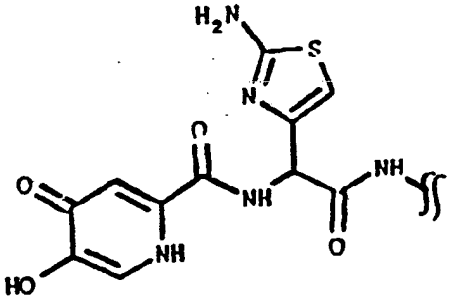


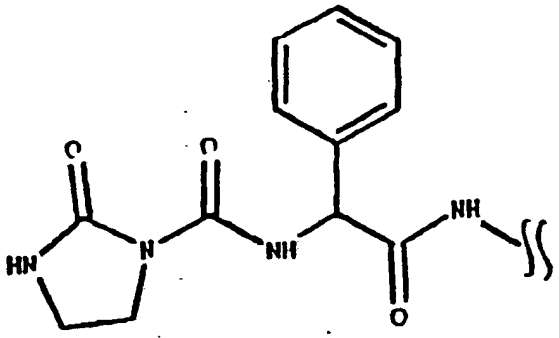
When R^1 is R^{13}-$(CH_2)_m$-C(=O)NH-, and R^{13} is -CH(Z^2)(R^{12}), preferred R^1 groups include the following:

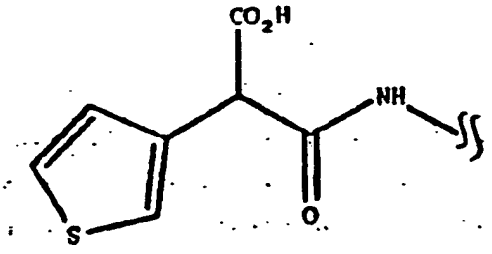
[carboxyphenylacetyl]amino;
[(phenoxycarbonyl)phenylacetyl]amino;
[4-methyl-2,3-dioxo-1-piperazinecarbonyl-D-phenylglycyl]-amino;
[[[3-(2-furylmethyleneamino)-2-oxo-1-imidazolidinyl]-carbonyl]amino]phenyl]acetyl]amino;
(R)-[(aminophenylacetyl)amino];
(R)-[[amino(4-hydroxyphenyl)acetyl]amino];
(R)-[(amino-1,4-cyclohexadien-1-ylacetyl)amino];
[(hydroxyphenylacetyl)amino];
(R)-[[[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]amino]-(4-hydroxyphenyl)acetyl]amino];
(R)-[[[[(5-carboxy-1H-imidazol-4-yl)carbonyl]amino]phenyl-acetyl]amino];
(R)-[[[[(4-hydroxy-6-methyl-3-pyridinyl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino];
(R)-[(phenylsulfoacetyl)amino];
(2R,3S)-[[2-[[(4-ethyl-2,3-dioxo-1-piperazinyl)carbonyl]-amino]-3-hydroxy-1-oxobutyl]amino];
[[carboxy(4-hydroxyphenyl)acetyl]amino];
(R)-[[amino[3-[(ethylsulfonyl)amino]phenyl]acetyl]amino];
(R)-[[amino(benzo[b]thien-3-yl)acetyl]amino];
(R)-[[amino(2-naphthyl)acetyl]amino];
(R)-[[amino(2-amino-4-thiazolyl)acetyl]amino];
[[[[(6,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl)carbonyl]-amino](4-hydroxyphenyl)acetyl]amino];
(R,R)-[[2-[4-[2-amino-2-carboxyethyloxycarbonyl]aminophen-yl]-2-hydroxyacetyl]amino]; and
(S)-[[(5-hydroxy-4-oxo-1(4H)-pyridin-2-yl)carbonylamino(2-amino-4-thiazolyl)acetyl]amino].

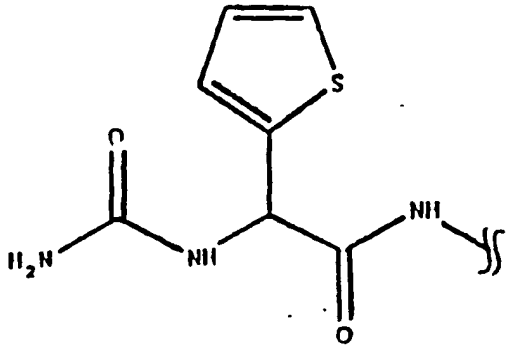
The following are other such preferred R^1 groups.

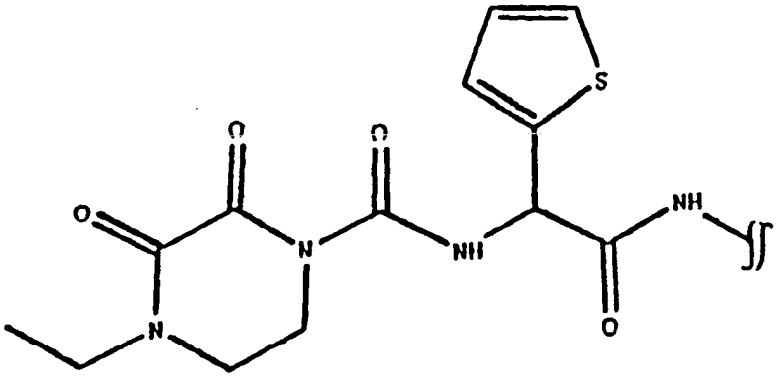


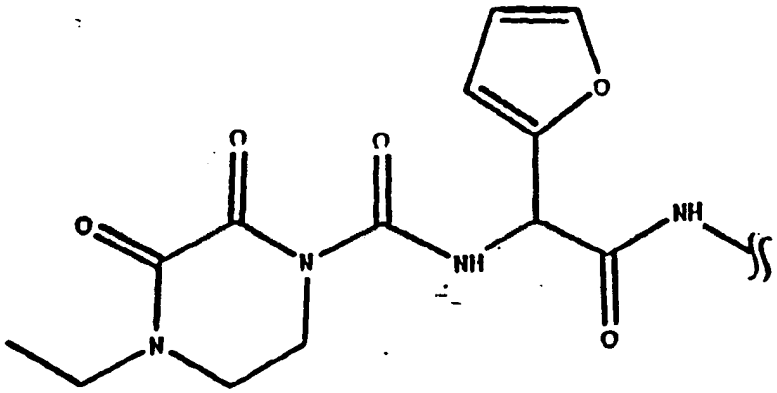


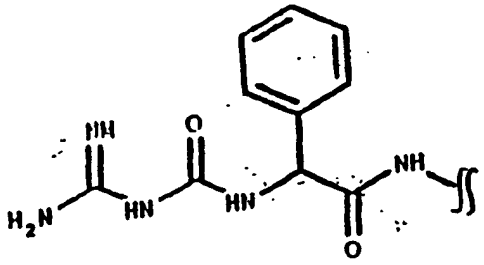


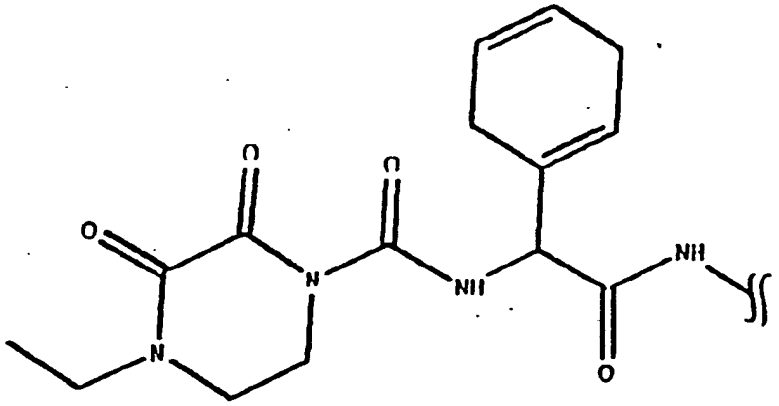


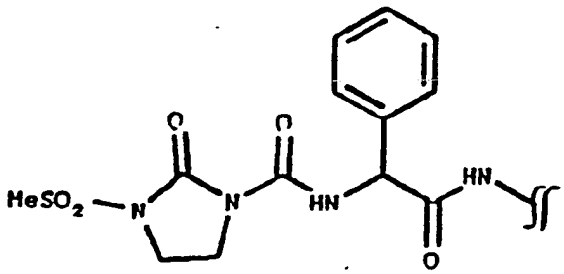


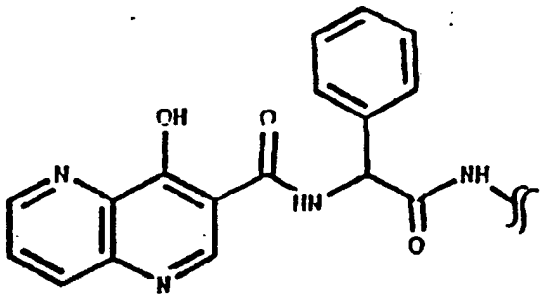


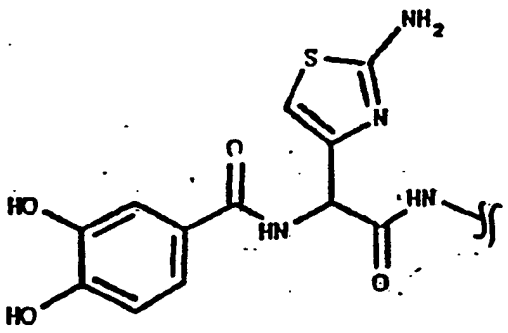


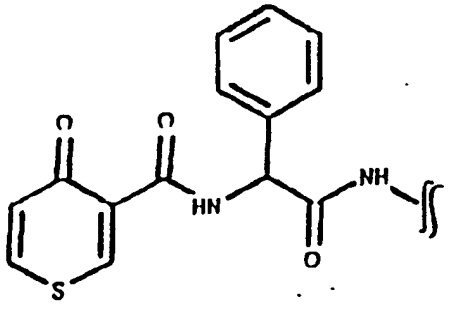


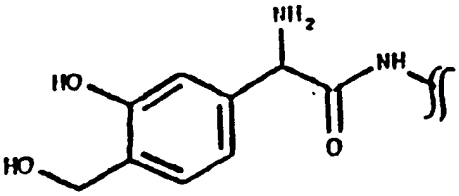


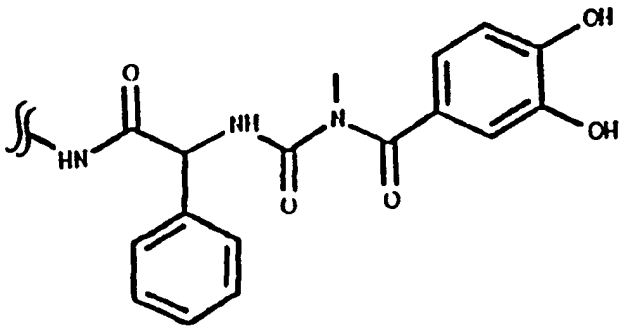


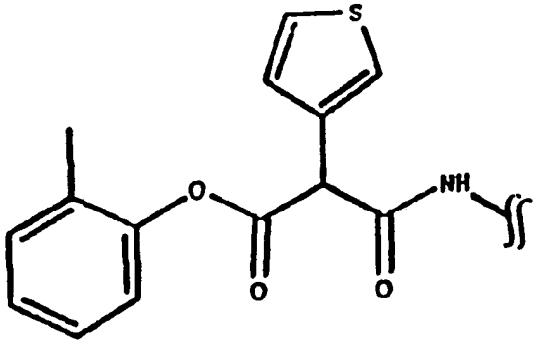


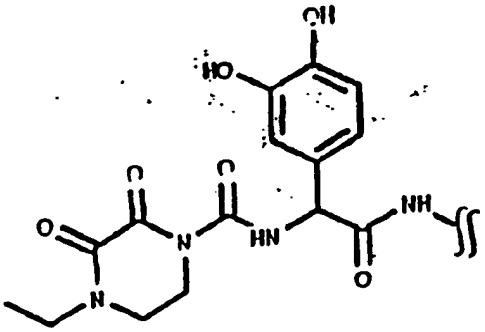


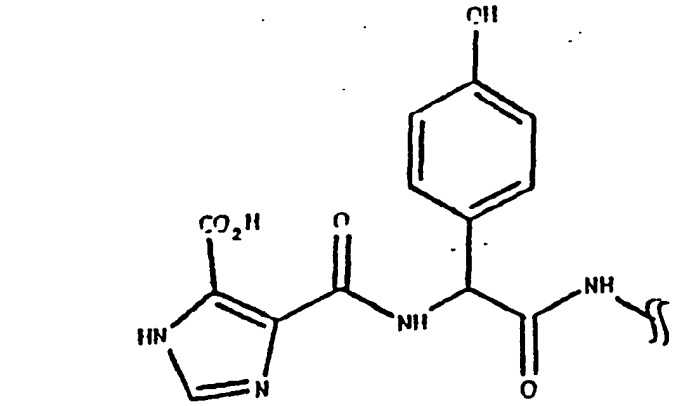


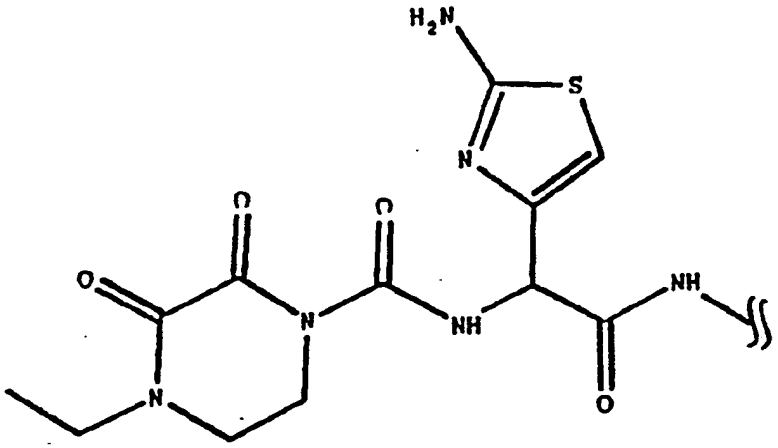




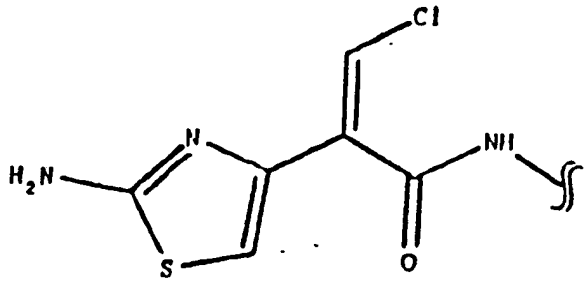


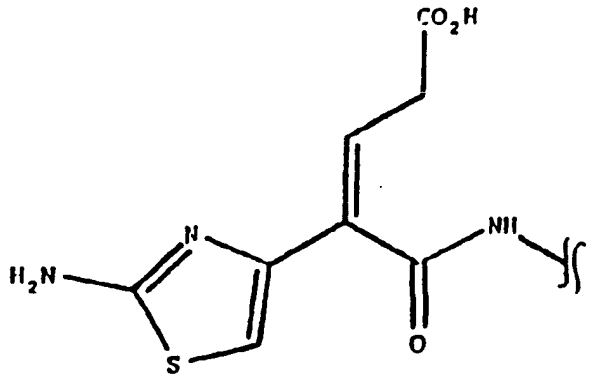






Another preferred R^1 group is R^{12}-C(=CHR^{15})-C(=O)NH-. Such groups include (for example) the following structures.





Another class of preferred R^1 groups include those of the formula:

$$R^{12}\text{-}C(=NO\text{-}R^{14})\text{-}C(=O)NH\text{-}.$$

Examples of this preferred class of R^1 groups include:

2-phenyl-2-hydroxyiminoacetyl;

2-thienyl-2-methoxyiminoacetyl;

2-[4-(gamma-D-glutamyloxy)phenyl]-2-hydroxyiminoacetyl;

(Z)[[(2-amino-4-thiazolyl)(methoxyimino)acetyl]amino];

[[(2-furanyl(methoxyimino)acetyl]amino];

(Z)-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methyl)ethoxyimino]acetyl]amino];

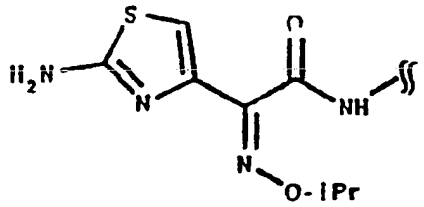
(Z)-[[(2-amino-4-thiazolyl)(1-carboxymethoxyimino)acetyl]amino];

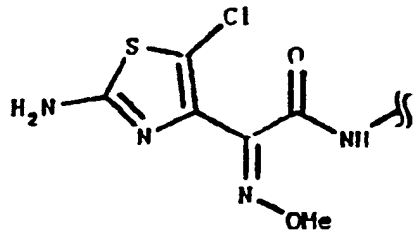
[[(2-amino-4-thiazolyl)[(1H-imidazol-4-ylmethoxy)imino]acetyl]amino];

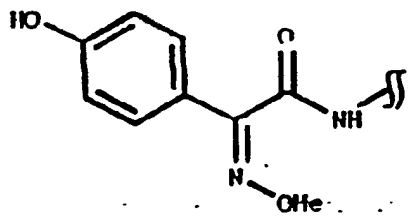
(Z)-[[(2-amino-4-thiazolyl-3-oxide)(methoxyimino)acetyl]amino]; and

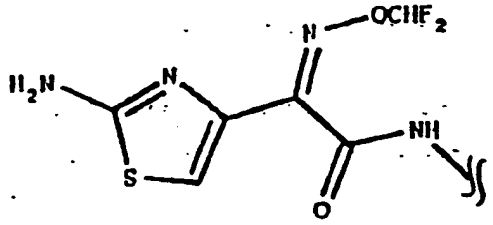
(S,Z)-[[(2-amino-4-thiazolyl)[carboxy(3,4-dihydroxyphenyl)methoxyimino]acetyl]amino].

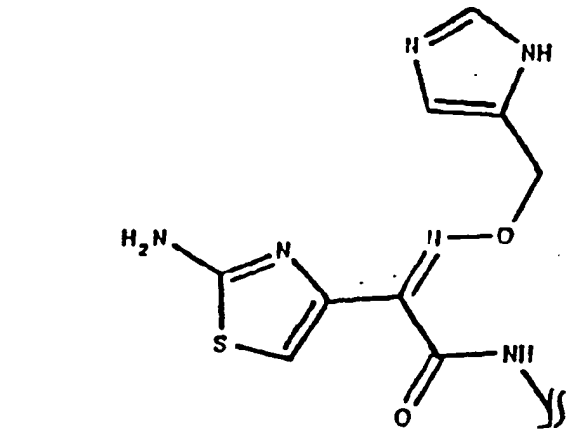
Other such preferred R^1 groups include the following structures.

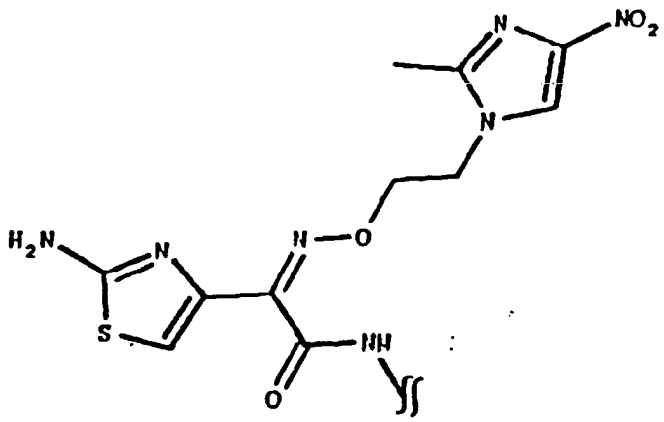


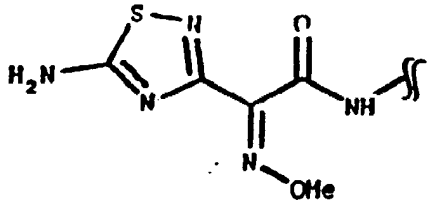


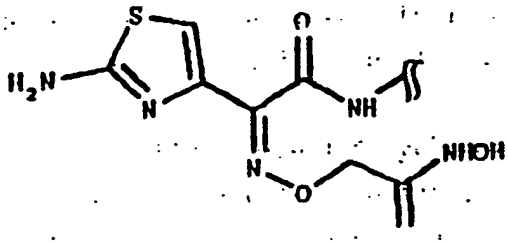


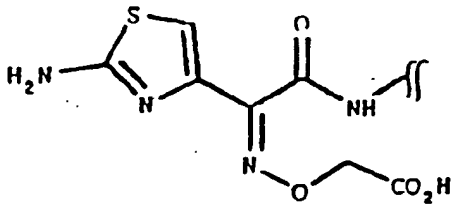


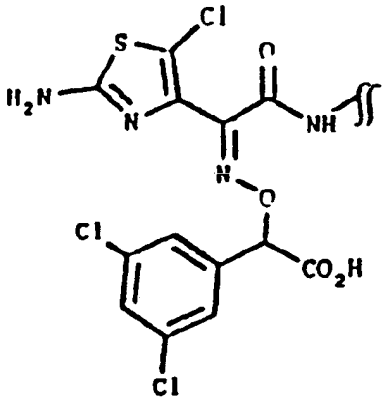


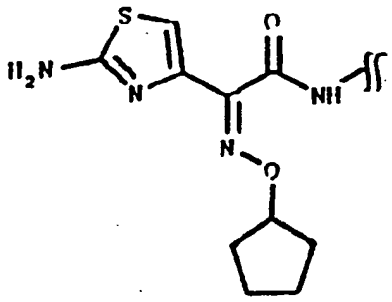


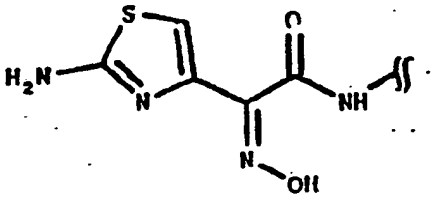


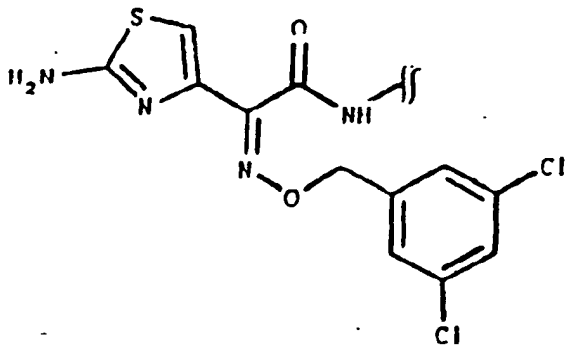


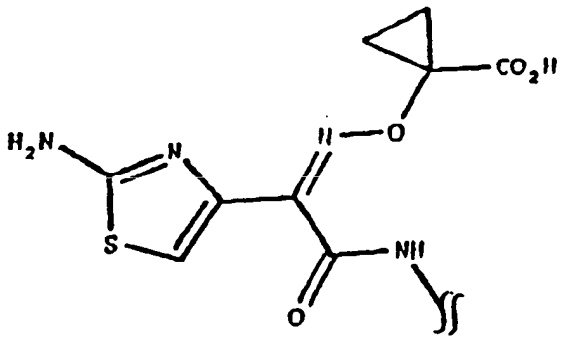




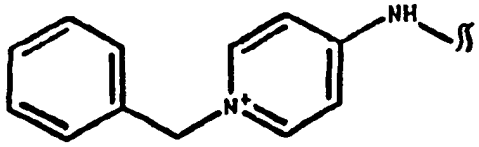


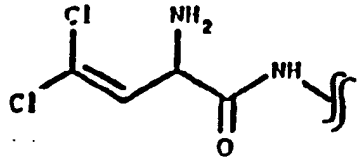


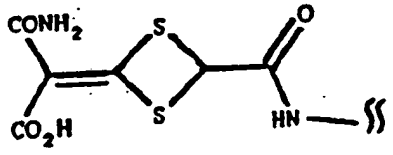


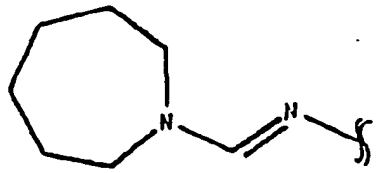


The following are other preferred R^1 groups.





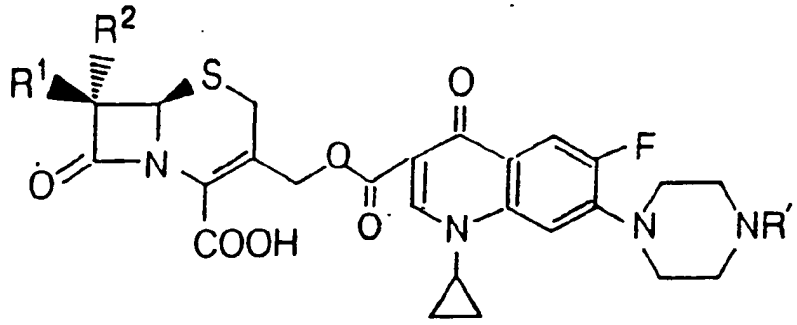




Suitable R^2 groups are among those well-known in the art, including those defined in the following documents (all incorporated by reference herein). W. Durckheimer et al., "Recent Developments in the Field of Beta-Lactam Antibiotics", 24 Angew. Chem. Int. Ed. Engl. 180 (1985); G. Rolinson, "Beta-Lactam Antibiotics", 17 J. Antimicrobial Chemotherapy 5 (1986); and European Patent Publication 187,456, Jung, published July 16, 1986. Preferred R^2 groups include hydrogen, methoxy, ethoxy, propoxy, thiomethyl, halogen, cyano, formyl and formylamino. Particularly preferred R^2 groups include hydrogen, methoxy, halogen, and formylamino.

Preferred R^3 groups include nitrogen-containing heterocyclic rings having from 5 to 8 members. The heterocyclic ring may contain additional heteroatoms, such as oxygen, sulfur, or nitrogen, preferably nitrogen. Such heterocyclic groups are described in U.S. Patent 4,599,334, Petersen et al., issued July 8, 1986; and U.S. Patent 4,670,444, Grohe et al., issued June 2, 1987 (both incorporated by reference herein). Preferred R^3 groups include unsubstituted or substituted pyridine, piperidine, morpholine, diazabicyclo[3.1.1]heptane, diazabicyclo[2.2.1]heptane, diazabicyclo[3.2.1]octane, diazabicyclo[2.2.2]octane, thiazolidine, imidazolidine, pyrrole and thiamorpholine, as well as the following particularly preferred R^3 groups include piperazine, 3-methylpiperazine, 3-aminopyrrolidine, 3-aminomethylpyrrolidine, N,N-dimethylaminomethylpyrrolidine, N-methylaminomethylpyrrolidine, N-ethylaminomethylpyrrolidine, pyridine, N-methylpiperazine, and 3,5-dimethylpiperazine.

A preferred fluoroquinolonyl cephem of this invention has the following formula:

(II) 

wherein R^1 and R^2 are as defined above; and R' is hydrogen or alkyl. Preferably, R' is hydrogen or methyl.

Preferred fluoroquinolonyl cephems of this invention include (for example)

[6R-[6a,7b(Z)]]-7[[[(2-amino-4-thiazolyl)methoxyimino]-acetyl]-amino]-3-[[[[1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[carboxy(4-hydroxyphenyl)acetyl]amino]-3-[[[[1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[[[((R)-6,7-dihydroxy-4-oxo-4H-1-benzopyran-3-yl)carbonyl]amino](4-hydroxyphenyl)acetyl]amino]-3-[[[[1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(R)-amino(4-hydroxyphenyl)acetyl]amino]-3-[[[[1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-

piperazinyl)-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[2-[[((R)-4-ethyl-2,3-dioxo-1-piperazinyl)-carbonyl]amino]-(S)-3-hydroxy-1-oxobutyl]amino]-3-[[[[1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(4-pyridinylthio)acetyl]amino]-3-[[[[1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(2-amino-4-thiazolyl)acetyl]amino]-3-[[[[7-(3-amino-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[[[((R)-4-ethyl-2,3-dioxo-1-piperazinyl)-carbonyl]amino](4-hydroxyphenyl)acetyl]amino]-3-[[[[7-(3-amino-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo--quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b(Z)]]-7-[[(2-amino-4-thiazolyl)[(1-carboxy-1-methylethoxy]imino]acetyl]amino]-3-[[[[7-(3-amino-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(R)-amino-1,4-cyclohexadien-1-yl)acetyl]-amino]-3-[[[[7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-

3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b(Z)]]-7-[[2-furanyl(methoxyimino)acetyl]amino]-3-[[[[7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[[[((R)-4-hydroxy-6-methyl-3-pyridinyl)-carbonyl]amino](4-hydroxyphenyl)acetyl]amino]-3-[[[[7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(R)-amino(phenyl)acetyl]amino]-3-[[[[7-(3-aminomethyl-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,-4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(R)-phenyl(sulfo)acetyl]amino]-3-[[[[7-(3-aminomethyl-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b(Z)]]-7-[[(2-amino-4-thiazolyl-3-oxide)(methoxyimino)acetyl]amino]-3-[[[[7-(3-aminomethyl-1-pyrrolidinyl)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxo-3-quinolinyl]-carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[hydroxy(phenyl)acetyl]amino]-3-[[[[7-(3-aminomethyl-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b(Z)]]-7-[[(2-amino-4-thiazolyl)[(S)-carboxy(3,4-dihydroxyphenyl)methoxyimino]acetyl]amino]-3-[[[[7-(3-aminomethyl-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[[(cyanomethyl)thio]acetyl]amino]-3-[[[[7-(3-aminomethyl-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]-carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[(cyanoacetyl)amino]-3-[[[[8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(R)-amino(2-amino-4-thiazolyl)acetyl]amino]-3-[[[[8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b(Z)]]-7-[[(2-amino-4-thiazolyl)[(1H-imidazol-4-ylmethoxy)imino]acetyl]amino]-3-[[[[8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[(1H-tetrazol-1-ylacetyl)amino]-3-[[[[7-(3-amino-1-pyrrolidinyl)1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo--3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b(Z)]]-7-[[(2-amino-4-thiazolyl)(1-carboxymethoxyimino)acetyl]amino]-3-[[[[7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]-

carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[2-[(R)-4-[2-amino-2-carboxyethyloxycarbonyl]aminophenyl]-(R)-2-hydroxyacetyl]amino]3-[[[[7-(3-amino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo- 3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(3,5-dichloro-4-oxo-1(4H)-pyridinyl)-acetyl]amino]-3-[[[[7-(3-aminomethyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(R)-amino(2-naphthyl)acetyl]amino]-3-[[[[7-(3-aminomethyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]-methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[[((S)-2-amino-2-carboxyethyl)thio]acetyl]amino]-3-[[[[7-(3-aminomethyl-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]-oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[[(R)-[(5-carboxy-1H-imidazol-4-yl)carbonyl]amino]phenylacetyl]amino]-3-[[[[7-(3-amino-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[[(trifluoromethyl)thio]acetyl]amino]-3-[[[[7-(3-amino-1-pyrrolidinyl)-8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]-

methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(R)-(5-hydroxy-4-oxo-1(4H)-pyridin-2-yl)-carbonylamino(2-amino-4-thiazolyl)acetyl]amino]-3-[[[[7-(3-amino-1-pyrrolidinyl)-38-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo--quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(R)-amino[3-[(ethylsulfonyl)amino]phenyl]-acetyl]amino]3-[[[[8-chloro-1-cyclopropyl7-[3-(ethylamino)-methyl-1-pyrrolidinyl]--6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo-[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[(R)-amino(benzo[b]thien-3-yl)acetyl]amino]-3-[[[[8-chloro-1-cyclopropyl7-[3-(ethylamino)-methyl-1-pyrrolidinyl]--6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid;

[6R-[6a,7b(R*)]]-7-[[amino[3-[(ethylsulfonyl)amino]phenyl]-acetyl]amino]-3-[[[[8-chloro-1-cyclopropyl7-[3-(ethylamino)-methyl-1-pyrrolidinyl]--6-fluoro-1,4-dihydro-4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]-oct-2-ene-2-carboxylic acid;

[6R-[6a,7b]]-7-[[[2-(aminomethyl)phenyl]acetyl]amino]-3-[[[[8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro7-(4-methyl-1-piperazinyl)--4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid;

[6R-[6a,7b(E)]]-7-[[[(2-aminocarbonyl-2-fluoroethenyl)thio]-acetyl]amino]-3-[[[[8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)--4-oxo--

3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo [4.2.0]oct-2-ene-2-carboxylic acid; and

[6R-[6a,7b]]-7-[[[(4-(2-amino-1-carboxy-2-oxoethylidene)-1,3-dithietan-2-yl]carbonyl]amino]-3-[[[[8-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-7-(4-methyl-1-piperazinyl)--4-oxo-3-quinolinyl]carbonyl]oxy]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Methods of Manufacture:

The fluoroquinolonyl cephems of this invention may be made by the following general reaction sequence:

$$Ceph\text{-}CH_2\text{-}X + M^{+-}OC(=O)\text{-}Quin \dashrightarrow Ceph\text{-}CH_2\text{-}OC(=O)\text{-}Quin$$

where X is a reactive leaving group (such as halo, a sulfonate ester or other activated hydroxyl functionality), "Ceph" generically represents an appropriately protected cephalosporin and "Quin" represents an appropriately protected quinolone. The reaction can be envisioned as a nucleophilic displacement of the reactive X substituent from the cephalosporin by the quinolone carboxylic acid or salt, to form an ester coupled conjugate of the cephalosporin and quinolone.

For Ceph and Quin, certain functional groups contained in the structures (such as carboxyl, hydroxyl, and amino groups) may need to be blocked in order to prevent undesired, competing side reactions with X. For example, suitable protecting groups for carboxyl substituents include esters; protecting groups for hydroxyl substituents include ethers, esters, and carbonates; and protecting groups for amino substituents include carbamates, amides, and carbonates. If such protecting groups are employed, then appropriate deprotecting chemistry, that will not decompose the ester coupled conjugate, may be required to obtain antimicrobially active products.

Depending on the R^1 group desired, the cephalosporin starting material may be available from any of a variety of commercial sources. Synthetic methods for producing such beta-lactams are well-known in the chemical literature. See, for example, Antibiotics, Chemotherapeutics, and Antibacterial Agents for Disease Control, pages 107-125 (M. Grayson, editor, 1982), incorporated by reference herein. The cephalosporin starting material can be esterified and converted to the 10-iodo derivative by methods well-known in the art. The fluoroquinolone starting material may also be commercially available (e.g., 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, known as "ciprofloxacin"). Syntheses of fluoroquinolones are described in U.S. Patent 4,670,444, Grohe et al., issued June 2, 1987 (incorporated by reference herein). The quinolone starting material may be made with appropriate protecting groups, by methods well-known in the art. For example, the piperazine nitrogen of ciprofloxacin can be readily converted to an alkyl carbamate.

Compositions:

The compositions of this invention comprise:

(a) a safe and effective amount of a fluoroquinolonyl cephem; and

(b) a pharmaceutically-acceptable carrier.

A "safe and effective amount" of a fluoroquinolonyl cephem is an amount that is effective, to inhibit microbial growth at the site of an infection to be treated in a human or lower animal subject, without undue adverse side effects (such as toxicity, irritation, or allergic response), commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such factors as the particular condition being treated, the physical condition of the patient, the duration of treatment, the nature of concurrent therapy (if any), the specific dosage form to be used, the carrier employed, the solubility of the

fluoroquinolonyl cephem therein, and the dosage regimen desired for the composition.

The compositions of this invention are preferably provided in unit dosage form. As used herein, a "unit dosage form" is a composition of this invention containing an amount of a fluoroquinolonyl cephem that is suitable for administration to a human or lower animal subject, in a single dose, according to good medical practice. These compositions preferably contain from about 30 mg to about 20,000 mg, more preferably from about 50 mg (milligrams) to about 7000 mg, more preferably from about 500 mg to about 1500 mg, of a fluoroquinolonyl cephem.

The compositions of this invention may be in any of a variety of forms, suitable (for example) for oral, rectal, topical or parenteral administration. Depending upon the particular route of administration desired, a variety of pharmaceutically-acceptable carriers well-known in the art may be used. These include solid or liquid fillers, diluents, hydrotropes, surface-active agents, and encapsulating substances. Optional pharmaceutically-active materials may be included, which do not substantially interfere with the antimicrobial activity of the fluoroquinolonyl cephem. The amount of carrier employed in conjunction with the fluoroquinolonyl cephem is sufficient to provide a practical quantity of material for administration per unit dose of the fluoroquinolonyl cephem. Techniques and compositions for making dosage forms useful in the methods of this invention are described in the following references, all incorporated by reference herein: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2d Edition (1976).

In particular, pharmaceutically-acceptable carriers for systemic administration include sugars, starches, cellulose and its derivatives, malt, gelatin, talc, calcium sulfate, vegetable oils, synthetic oils, polyols, alginic acid, phosphate buffer solutions, emulsifiers, isotonic saline, and pyrogen-free water. Preferred carriers for parenteral administration include

propylene glycol, ethyl oleate, pyrrolidone, ethanol, and sesame oil. Preferably, the pharmaceutically-acceptable carrier, in compositions for parenteral administration, comprises at least about 90% by weight by the total composition.

Various oral dosage forms can be used, including such solid forms as tablets, capsules, granules and bulk powders. These oral forms comprise a safe and effective amount, usually at least about 5%, and preferably from about 25% to about 50%, of the fluoroquinolonyl cephem. Tablets can be compressed, tablet triturates, enteric-coated, sugar-coated, film-coated, or multiple-compressed, containing suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Liquid oral dosage forms include aqueous solutions, emulsions, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules, and effervescent preparations reconstituted from effervescent granules, containing suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, melting agents, coloring agents and flavoring agents. Preferred carriers for oral administration include gelatin, propylene glycol, cottonseed oil and sesame oil.

The compositions of this invention can also be administered topically to a subject, i.e., by the direct laying on or spreading of the composition on the epidermal or epithelial tissue of the subject. Such compositions include, for example, lotions, creams, solutions, gels and solids. These topical compositions preferably comprise a safe and effective amount, usually at least about 0.1%, and preferably from about 1% to about 5%, of the fluoroquinolonyl cephem. Suitable carriers for topical administration preferably remain in place on the skin as a continuous film, and resist being removed by perspiration or immersion in water. Generally, the carrier is organic in nature and capable of having dispersed or dissolved therein the fluoroquinolonyl cephem. The carrier may include pharmaceutically-acceptable emolients, emulsifiers, thickening agents, and solvents.

Methods of Administration:

This invention also provides methods of treating or preventing an infectious disorder in a human or other animal subject, by administering a safe and effective amount of a fluoroquinolonyl cephem to said subject. As used herein, an "infectious disorder" is any disorder characterized by the presence of a microbial infection. Preferred methods of this invention are for the treatment of bacterial infections. Such infectious disorders include (for example) central nervous system infections, external ear infections, infections of the middle ear (such as acute otitis media), infections of the cranial sinuses, eye infections, infections of the oral cavity (such as infections of the teeth, gums and mucosa), upper respiratory tract infections, lower respiratory tract infections, genitourinary infections, gastrointestinal infections, gynecological infections, septicemia, bone and joint infections, skin and skin structure infections, bacterial endocarditis, burns, antibacterial prophylaxis of surgery, and antibacterial prophylaxis in immunosuppressed patients (such as patients receiving cancer chemotherapy, or organ transplant patients).

The fluoroquinolonyl cephems and compositions of this invention can be administered topically or systemically. Systemic application includes any method of introducing the fluoroquinolonyl cephem into the tissues of the body, e.g., intrathecal, epidural, intramuscular, transdermal, intravenous, intraperitoneal, subcutaneous, sublingual, rectal, and oral administration. The specific dosage of antimicrobial to be administered, as well as the duration of treatment, are mutually dependent. The dosage and treatment regimen will also depend upon such factors as the specific fluoroquinolonyl cephem used, the resistance pattern of the infecting organism to the fluoroquinolonyl cephem used, the ability of the fluoroquinolonyl cephem to reach minimum inhibitory concentrations at the site of the infection, the nature and extent of other infections (if any), the personal attributes of the subject (such as weight),

compliance with the treatment regimen, and the presence and severity of any side effects of the treatment.

Typically, for a human adult (weighing approximately 70 kilograms), from about 75 mg to about 30,000 mg, more preferably from about 100 mg to about 20,000 mg more preferably from about 500 mg to about 3500 mg, of fluoroquinolonyl cephem are administered per day. Treatment regimens preferably extend from about 3 to about 56 days, preferably from about 7 to about 28 days, in duration. Prophylactic regimens (such as avoidance of opportunistic infections in immunocompromised patients) may extend 6 months, or longer, according to good medical practice.

A preferred method of parenteral administration is through intramuscular injection. As is known and practiced in the art, all formulations for parenteral administration must be sterile. For mammals, especially humans, (assuming an approximate body weight of 70 kilograms) individual doses of from about 100 mg to about 7000 mg, preferably from about 500 mg to about 1500 mg, are acceptable.

A preferred method of systemic administration is oral. Individual doses of from about 100 mg to about 2500 mg, preferably from about 250 mg to about 1000 mg are preferred.

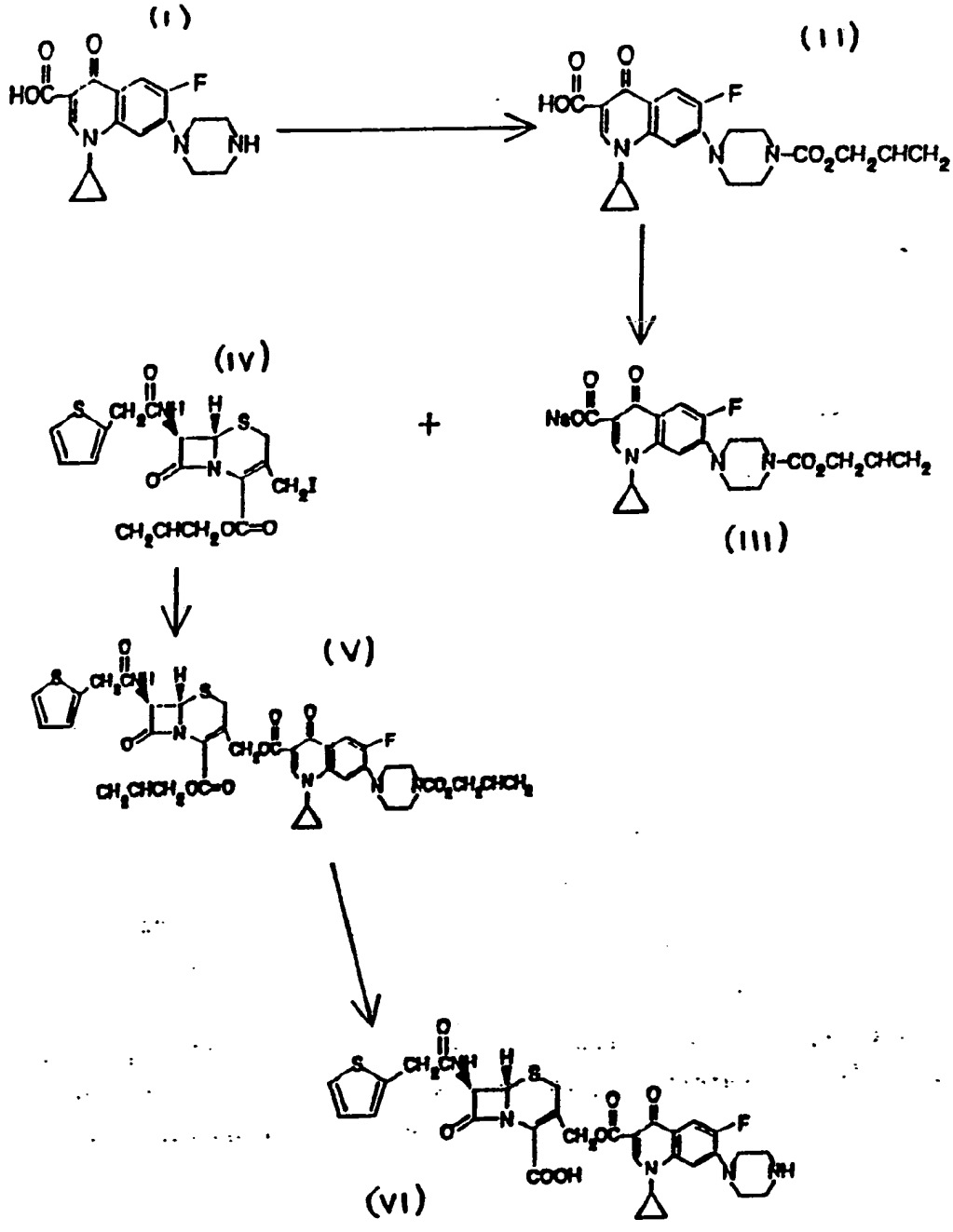
Topical administration can be used to deliver the fluoroquinolonyl cephem systemically, or to treat a local infection. The amounts of fluoroquinolonyl cephem to be topically administered depends upon such factors as skin sensitivity, type and location of the tissue to be treated, the composition and carrier (if any) to be administered, the particular fluoroquinolonyl cephem to be administered, as well as the particular disorder to be treated and the extent to which systemic (as distinguished from local) effects are desired.

The following non-limiting examples illustrate the compounds, compositions, processes, and uses of the present invention.

EXAMPLE I

[6R-[6a,7b]]-3-[[1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyloxy]methyl]-8-oxo-7-[(2-thieny-

lacetyl)amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, according to this invention, is made by the following general reaction sequence.



Approximately 10 g of ciprofloxacin (I) is dissolved in approximately 352 ml (milliliters) of distilled water, and cooled to approximately 0°C (32°F). The pH is then raised to approximately pH 12 by adding 1N sodium hydroxide. While stirring, approximately 88 ml of acetone is added, followed by dropwise addition of approximately 5.3 g of allylchloroformate in approximately 65.9 ml of acetone. The temperature of the solution is maintained at approximately 0°C (32°F), and the pH is maintained at approximately 12 by addition of sodium hydroxide. The reaction is stirred approximately 60 minutes.

The acetone is then evaporated from the solution. The resulting aqueous solution is twice extracted with ether. The aqueous layer is cooled, and 10% hydrochloric acid added to lower the pH to approximately pH 2.0. The solution is then extracted three times with ethyl acetate, washed with water, dried, and evaporated to yield approximately 12 g of product (II).

This intermediate is dissolved in dichloromethane, and chilled to approximately 0°C (32°F). A solution is added dropwise, with stirring, containing approximately 1.45 g sodium hydroxide in approximately 5.0 ml methanol. Stirring is continued for approximately 60 minutes, while allowing the reaction mixture to warm to ambient temperature (approximately 21°C, 70°F). The solution is then evaporated, yielding a white solid which is triturated in ether, and collected to give approximately 11.9 g of product (III).

Separately, reactant (IV) is prepared by suspending approximately 50 g of commercially-available cephalothin, sodium salt in a mixture of DMF (dimethylformamide) (468 ml) and dioxane (375 ml). The mixture is cooled to approximately 3°C (37°F). Allyl iodide (13.2 ml, 0.144 mole) is added. The reaction is then stirred in the dark, under nitrogen, at room temperature for approximately 46 hours. This reaction mixture is poured into a mixture of saturated sodium chloride (1600 ml) and ethyl acetate (800 ml). Some solid sodium chloride is precipitated and filtered off. The layers formed are separated, and the aqueous

phase extracted with ethyl acetate. The organic solutions are combined, washed with saturated sodium chloride, water, 10% sodium bicarbonate, and then water. The solution is then dried, filtered and evaporated. The residue is triturated with ether, and a solid intermediate collected by filtration.

Approximately 19.3 g of this intermediate is dissolved in dry dichloromethane (960 ml) under nitrogen. Trimethylsilyl iodide (16.3 ml, 0.0709 mole, 1.6 eq) is added. The solution is stirred in the dark, at room temperature, until no more starting material remains (approximately 1.5 hours). The solution is then cooled in ice and 10% aqueous sodium thiosulfate solution (500 ml) is added slowly, keeping the temperature at 15°C (60°F) or below. The resulting layers are separated and the organic phase is washed with 10% aqueous sodium thiosulfate and water, dried, and filtered. Acetone is added to the filtrate and the solution is filtered, and washed with 5% acetone/dichloromethane. The filtrate is then evaporated to near dryness. The residue is stirred and hexane added, precipitating a solid. The solid is collected by filtration, washed with hexane, and dried yielding reactant (IV).

Approximately 4 g of reactant (IV) is dissolved in approximately 41.8 ml of a 50% DMF/dioxane mixture, at room temperature. Approximately 3.5 g of product II is added, with stirring, at ambient temperature. Stirring is continued for approximately 90 minutes, and the solution is cooled to approximately 5°C (41°F). The mixture is then extracted with ethyl acetate, recovering the organic layer. The solution is washed five times with cooled 0.14N sodium hydroxide and with water. The solution is dried and evaporated to yield approximately 3.9 g of product (V).

Approximately 1.0 g of this intermediate is dissolved in approximately 24 ml of dry dichloromethane, containing approximately 0.128 ml of distilled water and 18 mg (milligrams) bis(triphenylphosphine)palladium chloride. Approximately 0.76 ml of tributyltin hydride is added while maintaining a temperature of approximately 21°C (70°F), forming a precipitate. After rapidly stirring for approximately 5 minutes, the precipitate is

collected by filtration and dried. The precipitate is then triturated in acetone to yield approximately 328 mg of final product (VI).

EXAMPLE II

An antimicrobial composition for parenteral administration, according to this invention, is made comprising:

Component	Amount
[6R-[6a,7b]]-3-[[1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyloxy methyl]8-oxo-7-[(2-thienylacetyl)-amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid[1]	100 mg/ml carrier
Carrier:	
sodium citrate buffer with (percent by weight of carrier):	
lecithin	0.48%
carboxymethylcellulose	0.53
povidone	0.50
methyl paraben	0.11
propyl paraben	0.011

1: a fluoroquinolonyl cephem, made according to Example I

The above ingredients are mixed, forming a suspension. Approximately 2.0 ml of the suspension is systemically administered, via intramuscular injection, to a human subject suffering from a lower respiratory tract infection, with Streptococcus pneumoniae present. This dosage is repeated twice daily, for approximately 14 days. After 4 days, symptoms of the disease subside, indicating that the pathogen has been substantially eradicated.

EXAMPLE III

An enteric coated antimicrobial composition for oral administration, according to this invention, is made comprising the following core tablet composition:

Component	Amount (mg)
[6R-[6a,7b]]-3-[[1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinyl]carbonyl oxymethyl]--8-oxo-7-[(2-thienylacetyl)-amino]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid[1]	350.0
starch	30.0
magnesium stearate	5.0
microcrystalline cellulose	100.0
colloidal silicon dioxide	2.5
povidone	12.5

1: a fluoroquinolonyl cephem, made according to Example I

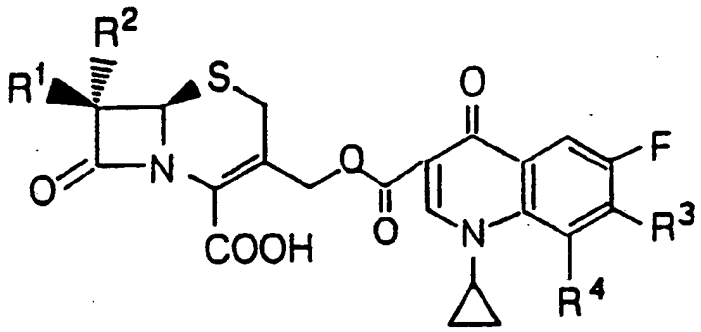
The components are admixed into a bulk mixture. Compressed tablets are formed, using tabletting methods known in the art. The tablets are then coated with a suspension of methacrylate acid/methacrylate ester polymer in isopropanol/acetone. A human subject, having a urinary tract infection with Escherichia coli present, is orally administered two of the tablets, every 8 hours, for 14 days. Symptoms of the disease then subside, indicating substantial eradication of the pathogen.

DLS/ewl/N526R(PA3)

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of the general formula

(I) 

wherein

(A) R^1 is hydrogen, halogen, alkyl, alkenyl, heteroalkyl, a carbocyclic ring, a heterocyclic ring, R^{10a}-O-, $R^{10a}CH$=N-, $(R^{10})(R^{11})$N-, R^{12}-C(=CHR^{15})-C(=O)NH-, R^{12}-C(=NO-R^{14})-C(=O)NH-, or R^{13}-$(CH_2)_m$-C(=O)NH-, preferably alkyl, alkenyl, R^{12}-C(=NO-R^{14})-C(=O)NH-, or R^{13}-$(CH_2)_m$-C(=O)NH-; where

(1) m is an integer from 0 to 9, preferably from 0 to 3;

(2) R^{10} and R^{11} are, independently, R^{10a} where R^{10a} is hydrogen, alkyl, alkenyl, a carbocyclic ring, or a heterocyclic ring substituent; or R^{10} and R^{11} together comprise a heterocyclic ring including the nitrogen to which they are bonded;

(3) R^{12} is hydrogen, alkyl, alkenyl, heteroalkyl, heteroalkenyl, a carbocyclic ring, or a heterocyclic ring, preferably alkyl, a carbocyclic ring or a heterocyclic ring;

(4) R^{13} is R^{12}, $-Z^1$, or $-CH(Z^2)(R^{12})$;

(5) R^{14} is R^{12}, arylalkyl, heteroarylalkyl, $-C(R^{17})(R^{18})COOH$, $-C(=O)O-R^{12}$, or $-C(=O)NH-R^{12}$, preferably R^{12} or $-C(R^{17})(R^{18})COOH$; where R^{17} and R^{18} are, independently, R^{12} or together comprise a

carbocyclic ring or a heterocyclic ring including the carbon atom to which R^{17} and R^{18} are bonded;

(6) R^{15} is R^{14}, halogen, $-Z^1$, or $-CH(Z^2)(R^{12})$, preferably R^{14} or halogen;

(7) Z^1 is $-C(=O)OR^{16}$, $-C(=O)R^{16}$, $-N(R^{19})R^{16}$, $-S(O)_pR^{24}$, or $-OR^{24}$; and Z^2 is Z^1 or -OH, -SH, or $-SO_3H$;

(a) p is an integer from 0 to 2, preferably 0;

(b) R^{19} is hydrogen; alkyl; alkenyl; heteroalkyl; heteroalkenyl; a carbocyclic ring; a heterocyclic ring; $-SO_3H$; $-C(=O)R^{20}$; or, when R^{13} is $-CH(Z^2)(R^{12})$ and Z^2 is $-N(R^{19})R^{16}$, R^{19} may comprise a moiety bonded to R^{16} to form a heterocyclic ring; and

(c) R^{20} is R^{12}, $NH(R^{12})$, $N(R^{12})(R^{21})$, $O(R^{21})$, or $S(R^{21})$, preferably R^{12}, $NH(R^{12})$, or $N(R^{12})(R^{21})$; where R^{21} is alkyl, alkenyl, a carbocyclic ring, a heterocyclic ring, or when R^{20} is $N(R^{12})(R^{21})$ R^{21} may be a moiety bonded to R^{12} to form a heterocyclic ring; and

(8) R^{16} is R^{24} or hydrogen, preferably hydrogen, alkyl, a carbocyclic ring or a heterocyclic ring; where R^{24} is alkyl; alkenyl; arylalkyl; heteroalkyl; heteroalkenyl; heteroarylalkyl; a carbocyclic ring; a heterocyclic ring; or, when Z^1 is $N(R^{19})R^{16}$ and R^{16} is R^{24}, R^{16} and R^{19} may together comprise a heterocyclic ring including the nitrogen atom to which R^{19} is bonded;

(B) R^2 is hydrogen, halogen, alkoxy, or $R^{22}C(=O)NH-$, preferably hydrogen or alkoxy; where R^{22} is hydrogen or alkyl;

(C) R^3 is a nitrogen-containing heterocyclic ring; and

(D) R^4 is hydrogen, hydroxy, alkoxy, nitro, cyano, halogen, alkyl or $N(R^{10})(R^{11})$;

and pharmaceutically-acceptable salts and biohydrolyzable esters thereof, and hydrates thereof.

2. A compound, according to Claim 1, wherein R^2 is hydrogen or alkoxy.

3. A compound, according to Claim 1, wherein R^4 is hydrogen or halo, preferably chlorine or fluorine.

4. A compound, according to Claim 3, wherein R^3 is piperazine, 3-methylpiperazine, 3-aminopyrrolidine, 3-aminomethylpyrrolidine, N,N-dimethylaminomethylpyrrolidine, N-methylaminomethylpyrrolidine, N-ethylaminomethylpyrrolidine, pyridine, N-methylpiperazine, or 3,5-dimethylpiperazine, preferably piperazine.

5. A composition for treating or preventing an infectious disorder in a human or other animal subject, comprising:

(1) a safe and effective amount of a compound of Claim 1, 2, 3 or 4; and

(2) a pharmaceutically-acceptable carrier.

6. A composition for treating or preventing an infectious disorder in a human or other animal subject, according to Claim 5, wherein said composition is suitable for parenteral administration.

7. A composition for treating or preventing an infectious disorder in a human or other animal subject, according to Claim 5, wherein said composition is suitable for oral administration.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US89/04768

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5) C07D501/48; A61K 31/545

US CL. 540/222; 540/226; 540/221; 514/205; 514/202

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	540/222; 540/225; 540/226; 540/227; 540/230 514/202; 514/205

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

C AS ON LINE (COMPUTER SEARCH)

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	JP, A, 56-5484 DAINIPPON PHARM KK, 20 January 1981, see entire document	
A	JP, A 56-5485 DAINIPPON PHARM KK, 20 January 1981, see entire document	

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
30 January 1990	09 MAR 1990

International Searching Authority	Signature of Authorized Officer
ISA/US	NICHOLAS S. RIZZO / app 2/8/90

Form PCT/ISA/210 (second sheet) (Rev.11-87)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers , because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international sparch can be carried out [13], specifically:

3. ☐ Claim numbers 1, because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

SEE ATTACHMENT

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

CLAIMS 1-7(IN PART)

4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM THE FIRST SHEET
(Not for publication)

INVITATION TO RESTRICT

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

GROUPING OF INVENTIONS

GROUP I. Cephem compounds of the type wherein R^1 and R^2 are not amino or acylamino(claims 1-7, in part).

GROUP II. Cepham Compounds of the type wherein R^1 is "acylated amino" (claims 1-7, in part).

GROUP III. Cepham Compounds of thetype wherein R^1 is amino (claims 1-7, in part).

REASONS FOR HOLDING OF LACK OF UNITY OF INVENTION

The inventions listed as Groups I, II and III do not meet the requirements for Unity of Invention for the following reasons:

Each of thegroups lack "unity of invention" because of structural dissimilarity, each requires separate search in the literature in the patents and each is separately classified. Each requires separate and distinct considerations for patentability and each will support separate patents.

TELEPHONE ELECTION, SINGLE INVENTION

During a telephonic requirement for election, on January 3, 1990 applicant's representative, Mr. Witte, elected the invention of Group II for examination.
No additional fees were authorized and only one invention was elected.